RESPONSE

I. Status of the Claims

Claims 1, 2 and 6-9 are presently pending in this case.

II. Rejection of Claims Under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph

The Action rejects all claims under 35 U.S.C. § 101 and under 35 U.S.C. § 112, first paragraph, allegedly because the claimed invention lacks support by either a specific and substantial asserted utility or a well established utility. Applicants respectfully traverse.

The Examiner discounts many of the numerous utilities described in the specification for the claimed sequences of the present invention based on the position that while credible, these utilities are not specific or substantial. While Applicants in no way agree with the Examiner's arguments, Applicants have chosen to expand on only a few of the utilities presented as only one is required and incorporate by reference those made in earlier responses.

Further, based on the statement "The claimed invention in the instant case is drawn to nucleic acid sequences, not a device" (Action page 9, lines 14-17) , it appears that the Examiner is of the opinion that the various mandatory legal precedents provided in Federal Circuit decisions are narrowly limited to the particular technologies discussed in each specific case. If this were indeed true, which is clearly not the case, the Federal Circuit's various articulations of the legal standards for utility, enablement, doctrine of equivalents, etc., for juice dispenser inventions, for example, would have virtually no bearing on similar legal inquiries relating to electrical inventions, business methods, or inventions from distinct arts. Applicants again contend that the Examiner's articulated position lacks any legal and procedural foundation and is intellectually unsound. Indeed, one might presume to speculate that a Federal Circuit panel would find the Examiner's stated position as representing a rather remarkable deviation from established legal precedent.

Applicants respectfully submit that the legal test for utility involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. According to the Examination Guidelines for the Utility Requirement,

if the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 Federal Register 1098, January 5, 2001).

In *In re Brana,* (34 USPQ2d 1436 (Fed. Cir. 1995), "*Brana*"), the Federal Circuit admonished the P.T.O. for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago.

Brana at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections under 35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between 35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and

development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted. In assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (C.C.P.A. 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Even under the newly installed utility guidelines, Applicants note that MPEP 2107 (II)(B)(1) states:

> (1) If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility. (MPEP 2107 (II)(B)(1))

The Examiner repeatedly argues that post filing documents cannot be used to support Applicants assertions of utility (see, for example, page5, line 15 and page 6, line 13). However, as summarized above, the question with regard to patentable utility is, did Applicants assert a credible utility in the specification. After filing evidence submitted by Applicants has been submitted to demonstrate that their assertions would be considered credible by a person of ordinary skill in the art. Applicants submit that the use of post filing evidence to clearly indicate that their assertions were credible is proper and correct.

Throughout the prosecution of this case, the Examiner has failed to submit any directly applicable objective evidence that Applicants' assertions were not credible and has chosen to discount Applicants evidence as irrelevant as it is post filing evidence. In contrast,

Applicants have submitted several forms of third party evidence that indeed indicate that those of skill in the art would have readily viewed both their identification and functional assertions as credible (for when faced with the same facts, others made the same assertions) and, thus, under the newly installed utility guidelines the Examiner has improperly imposed a rejection based on a lack of utility.

Applicants assertion of the stated utility is legally sufficient and should control the utility analysis unless the Examiner meets the burden of establishing the lack of utility by making evidence of record that conclusively refutes the Applicants asserted utility. In the instant case no countervailing, specific evidence refuting Applicant's assertions has been presented. The Examiner has thus failed to meet the Office's initial burden of establishing a *prima facia* case with evidentiary support.

Applicants have submitted evidence that a sequence sharing greater than 93% identity at the amino acid level with the sequences of the present invention is present in the leading scientific repository for biological sequence data (GenBank), and has been annotated by third party scientists *wholly unaffiliated with Applicants* as *Homo sapiens* putative vascular inducible G protein-coupled receptor (VIGR) mRNA (GenBank accession number AAO13250, alignment and information provided previously). The legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. Given this GenBank annotation, there can be little question that those skilled in the art would clearly believe that Applicants' sequence is a novel human G protein-coupled receptor, as set forth in the specification as originally filed. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101

and 35 U.S.C. § 112, first paragraph.

The Action states that neither the specification not the art of record disclose any diseases or conditions associated with the function or expression of the NGPCR protein, therefore there is no "real world" context of use". Applicants' strongly disagree, as the specification details a number of specific and substantial utilities for this the presently claimed polynucleotide sequences, which encode a vascular inducible G protein-coupled receptor, were described in the specification (at page 4) as having utility in the detection and diagnosis of human diseases, *inter alia*, atherosclerosis, heart disease and abnormal blood pressure (all of which are vascular indications).

Further evidence of the physiologic importance of the molecules encoded by the sequences of the present invention was submitted in the form of results obtained in knockout mouse which were prepared as described at multiple locations within the specification (page 2, line 32 through page 3, line 6; page 4, line 4; page 6, line 6; page 26, lines 7-15). Knockout mice in which the mouse gene encoding the ortholog of SEQ ID NOS: 1 and 2 of the present invention was disrupted by homologous recombination (as described in the specification) and resulted in neonatal lethality and developmental abnormalities in the offspring. While mice heterozygous (+/-) exhibited slightly increased mean systolic blood pressures when compared with their gender-matched wild-type (+/+) littermates and the historical mean. This provides clear evidence that the nucleic acid and protein encoded by the sequences of the present invention have a critical biological role in vascular development. Clearly, the sequences of the present invention, the molecules which they encode and agonists or antagonists directed at them, can be used, as provided in the specification as filed, to

diagnose and treat vascular disorders such as, *inter alia*, atherosclerosis, heart disease, and specifically abnormal blood pressure (specification at page 4, lines 6-10). Thus the sequences of the present invention and the molecules which they encode represent biologically validated drug targets, a real world substantial and specific utility.

However, the Examiner has deemed these assertions to be without merit while failing to meet the Office's initial burden of establishing a *prima facia* case with evidentiary support that conclusively refutes the Applicants' asserted utility. Such evidence has not been provided, because it does not exist. Thus, the Examiner returns to the unrelated contrary art which does not refer to the molecules of the present invention and which was cited and dealt with previously. The Examiner again cites an article by Yan *et al.* ("Yan"; 2000, Science 290:523-527) for the proposition that "even a two-amino acid substitution in a molecular structure of a protein can lead to total loss of a protein (*sic*) to bind a specific receptor" (Action at page 4). However, this paper cites only <u>one</u> example, (which is a TNF receptor superfamily protein not a G-protein coupled receptor) two isoforms of the anhidrotic ectodermal dysplasia (EDA) gene, where a two amino acid change conforms one isoform (EDA-A1) into the second isoform (EDA-A2). However, while it is true that this amino acid change results in binding to different receptors, it is important to note that the different receptors bound by the two isoforms are in fact <u>related</u> (Yan at page 523). Furthermore, the EDA-A2 receptor was correctly identified as a member of the tumor necrosis factor receptor superfamily based <u>solely on sequence similarity</u> (Yan at page 523). Thus, Yan is hardly indicative of a high level of uncertainty in assigning function based on sequence, and thus also does not support the alleged lack of utility.

In the Final Action the Examiner also provided additional articles that allegedly argue against the value of structure-function relationships. The Final Action (on page 4, lines 13-14) asserts that based on the introduction to a 17 year old article that "one cannot assume *a priori* that such change will not significantly alter the properties of a protein". First, Applicants note that the state of the art, and the reliability of its methodologies have progressed significantly in the 17 years since this article was published. Second, Applicants believe that those of skill in the art would readily recognize that one cannot assume *a priori* that such a change would significantly alter the properties of a protein either, as many amino acid substitutions do not effect function, particularly when like amino acids are involved.

The Examiner again next cites Doerks *et al.* (Trends in Genetics *14*:248-250, 1998) in support that sequence-to-function methods of assigning protein function are prone to errors due to partial annotation, multifunctionality and over prediction. However, Doerks *et al.* states that "utilization of family information and thus a more detailed characterization" should lead to "simplification of update procedures for the entire families if functional information becomes available for at least one member" (Doerks *et al.*, page 248, paragraph bridging columns 1 and 2, emphasis added). Applicants point out that GABA receptor proteins represent a very well-studied protein family with a large amount of known functional information, exactly the situation that Doerks *et al.* suggests will "simplify" and "avoid the pitfalls" of previous sequence-to-function methods of assigning protein function (Doerks *et al.*, page 248, columns 1 and 2). Thus, instead of supporting the Action's position against utility, Doerks *et al.* supports Applicants' position that the presently claimed sequences have a well-established utility.

The Examiner also again cites Brenner (Trends in Genetics *15*:132-133, 1999) as teaching that proposition that accurate inference of function from homology is a difficult problem . However, this statement is based on the assumption that "if there are only 1000 superfamilies in nature, then most homologs must have different molecular and cellular functions" (page 132, second column). Furthermore, Brenner suggests that one of the main problems in using homology to predict function is "an issue solvable by appropriate use of modern and accurate sequence comparison procedures" (page 132, second column), and in fact references an article by Altschul *et al.*, which is the basis for one of the "modern and accurate sequence comparison procedures" used by Applicants. Thus, the Brenner article also does not support the alleged lack of utility.

The Examiner next again cites Bork (Genome Research *10*:398-400, 2000) as supporting the proposition that prediction of protein function from homology information is somewhat unpredictable. The Action directs attention to page 399, on which the author notes the limitations of various methods of analysis. It is of interest that in his "analysis" Bork often uses citations to many of his own previous publications, an interesting approach. ' My position is supported by my previous disclosures of my position.' If Bork's position is supported by others of skill in the art, one would expect that he would reference them rather than himself to provide support for his statements. Given that the standard with regard to obtaining U.S. patents is those of skill in the art, this observation casts doubt on the broad applicability of Bork's position. I t should also be noted that in Table 1,on page 399, in which selected examples of prediction accuracy are presented, that the reported accuracy of the methods which Applicants have employed are, in fact, very high. While nowhere in Bork

is there a comparison of the prediction accuracy based on the percentage homology between two proteins or two classes of proteins, "Homology (several methods)" is assigned an accuracy rate of 98% and "Functional features by homology" is assigned an accuracy rate of 90%. Given that these figures were obtained based on what is at least a 4 year old analysis, these high levels of accuracy would appear to support rather than refute Applicants assertions in the present case. Additionally Bork even states (on page 400, second column, line 17) that " However, there is still no doubt that sequence analysis is extremely powerful". In summary, it is clear that it is not Bork's intention to refute the value of sequence analysis but rather he is indicating that there is room for improvement .

Finally, the Examiner also again cites Bork, *et al.* (Trends in Genetics *12*:425-427, 1996) as supporting the proposition that prediction of protein function from homology information is somewhat unpredictable. The question as to whether Bork's positions are generally supported by those of skill in the art was discussed above in the paragraph regarding the other Bork citation. It should also be noted that this article was published approximately 6 years ago and thus refers to errors or "traps" associated with earlier algorithms and technologies in a field that has undergone constant improvement. This publication identifies (Table 1) various areas in which incorrect information appears in sequence databases. These "traps" include Synonyms - a single gene having a variety of names, Different gene-same name- when the same name is used to describe different genes, Spelling errors, Contamination-the unintentional inclusion of vector sequences, etc. and propagation of incorrect functional associations based on poorly analyzed homology. All of these issues can effect the accuracy of sequence base analysis, however all can be overcome by a more careful

analysis as would be done by one of skill in the art. Automatic methods of sequence homology as identified by any algorithm is a staring point for consideration, and one of skill in the art can then through further analysis, structure-function analysis, etc. can and should then verify the associations. For example in addition to algorithm based sequence analysis the sequences of the present invention underwent careful analysis by a series of individuals of skill in the art, many highly qualified (B.S. and Ph.D. level scientists). Clearly such highly skilled and careful analysis reduces the influence of such "traps". Furthermore, in the final section of this publication (page 427) it again becomes cleat that Bork, *et al.* do not discount the value of sequence analysis "we wish to point out that sequence database are the most useful tool in sequence analysis and the question should be how can one further improve their value". Thus clearly this publication represents a call to action to enhance the already high value of sequence analysis rather than an indictment of the utility of sequence based analysis. Therefore, as Bork, *et al.* identifies the high value of sequence based analysis it actually supports rather than refutes Applicants assertions regarding the utility of the present invention.

Thus, as previously stated, a careful reading of the cited "relevant literature" does not in fact support the concept that function cannot be based on sequence and structural similarity, in contrast many of the examples actually support the use of such methodologies while identifying several areas in which caution should be exercised. As stated previously these inaccuracies and potential pitfalls can be overcome by a more careful analysis by those of skill in the art. Automatic methods of sequence homology identification was only the staring point for consideration the sequences of the present invention underwent careful

analysis by a series of individuals of skill in the art, many highly qualified (B.S. and Ph.D. level scientists). These articles are just examples of the few contrarian articles that the PTO has repeatedly attempted to use to deny the utility of nucleic acid sequences based on a small number of publications that call into doubt prediction of protein function from homology information and the usefulness of bioinformatic predictions. While there may not be a 100% consensus within the scientific community regarding prediction of protein function from homology information this is not unusual, in the scientific community or the legal community for that matter, however it clearly is not indicative of a general lack of consensus. The vast majority of those of skill accept the concept that there is a structure function relationship. A few rare exceptions do not a rule make.

In the present case, clearly evidence supports Applicants' assertions that the sequences of the present invention encode human GPR proteins, a protein for which there is a well established utility that is recognized by those of skill in the art and whose asserted involvement in human vascular disease would have clearly been credible to those of skill in the art at the time the application was filed.

The Action, in the final paragraph of page 10, cites *Brenner v Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966), for noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." Applicants whole heartedly agree and note that the search for the sequences that are the claimed invention of the present application is over. Applicants were the first to have successfully concluded the search for the presently claimed novel human G protein-coupled receptor sequences and the results of this search have been clearly listed in the Sequence Listing of the instant

application. No further "hunting" is required. As Applicants have brought this search to its successful conclusion, they are due the reward, a U.S. Patent claiming the results of their difficult but successful efforts. Thus, Applicants respectfully request the withdrawal of the rejection of the claimed sequences under 35U.S.C. § 101 and 35 U.S.C. § 112, first paragraph.

Finally it must be noted that it appears that one of the intent of the New Utility Guidelines was to be to align U.S. patent law with that of the rest of the world. But clearly the new Utility Guidelines fail in this regard, for the European Patent Office has determined that in view of the prior art that the identification of novel human G protein-coupled receptor sequences, have so much recognized utlity as to be rendered obvious and therefore such an identification requires no inventive skill. If an invention is deemed so obvious and requires no inventive step, then clearly it must have a recognized utility and satisfy the requirements under 35U.S.C. § 101 and 35 U.S.C. § 112, first paragraph.

III. **Rejection of Claims Under 35 U.S.C. § 112, First Paragraph**

The Action also rejects claims 7 and 9 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which is not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is well established that the PTO carries the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); MPEP § 2164.04. Further the enablement

requirement is satisfied if the specification describes any method for making and using the claimed invention that bears a "reasonable correlation" to the entire scope of the claims. *Id.* at 839, 166 USPQ at 24.

While it is the role of the examiner to first construe the claims. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970). Applicants' respectfully submit that as defined in MPEP § 2164.04 in order to make a rejection, the examiner has the initial burden to establish (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). In the present case the Examiner has submitted a chapter authored by Eck & Wilson, that appears in the ninth edition of Goodman & Gillman's The Pharmacological Basis of Therapeutics (1996). The Eck & Wilson chapter refers to gene therapy as practiced at least six years before the present application was filed. Text books, such as Goodman & Gillman require extensive compilation and editing and as a result are often out of date by the time they publish. Thus, the Eck & Wilson chapter regarding gene therapy, more likely relates to the state of gene therapy more than 6 years prior to the filing date of the present application and thus does not accurately represent the state of the art at the time the present application was filed. The submitted reference is directed not at the claimed invention, but a process in which the claimed invention might be used, thus this reference cannot reasonably be used to support a *prima facia* case against the presently claimed invention. For the record, though irrelevant to the instant case, gene therapy has been successful in some cases.

However, more germane to the present rejection is the fact that the rejected claims are not directed at gene therapy, but a host cell. The present application is fully enabling for the claimed invention - a host cell. Many host cells are described in the specification as filed and host cells

are very well known to those of skill in the art. Perhaps it is true that a host cell can be used in gene therapy and perhaps such a use might require additional experimentation and perhaps the present application would not be found to enable gene therapy. All of this is irrelevant, the claims of the present invention are not directed at gene therapy or the use of a host cell. The claims of the present invention are directed at a host cell comprising a particular vector. Applicants note that the present specification is also not enabling for the use of a host cell on the moon, but that is also irrelevant to a claim directed at a host cell itself. Because, like gene therapy, the use of a host cell on the moon would not properly be interpreted to fall within the scope of the present claims which are directed at a host cell, not its use on the moon.

In addition, it must be noted that claims direct at a "host cell" have been allowed in hundreds of patents which contain no more disclosure than the present case (see for example U.S. Patent Nos. 6,531,309, 6,586,230, 6,777,221: **Exhibits V-X**, copies of issued U.S. Patents not provided pursuant to current United States Patent and Trademark Office policy). As issued U.S. Patents are presumed to meet all of the requirements for patentability, including enablement under 35 U.S.C. §112, first paragraph. Therefore, Applicants respectfully submit that the presently claimed host cell must also logically be enabled and meet the requirements of 35 U.S.C. § 112, first paragraph.

Furthermore, Applicants note that had their claims been directed at gene therapy, by definition gene therapy or any other process that would require "undue experimentation" would not properly be interpreted to fall within the scope of the present claims. The courts would recognize that as it is not enabled, such a subject does not falls within the reasonable scope of the present claims and any legal action based on such interpretation would be destined to failure.

In re Wands (8 USPQ 2d 1400 (Fed. Cir. 1988); "*Wands*") established the standards for the determination that a invention could not be practiced without "undue experimentation". However, it is important to remember that in assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976). In *Wands*, the P.T.O. took the position that the applicant failed to demonstrate that the disclosed biological processes of immunization and antibody selection could reproducibly result in a useful biological product (antibodies from hybridomas) within the scope of the claims. In its decision overturning the P.T.O.'s rejection, the Federal Circuit found that Wands' demonstration of success in four out of nine cell lines screened was sufficient to support a conclusion of enablement. The court emphasized that the need for some experimentation requiring, *e.g.*, production of the biological material followed by routine screening, was not a basis for a finding of non-enablement, stating:

> Disclosure in application for the immunoassay method patent does not fail to meet enablement requirement of 35 USC 112 by requiring 'undue experimentation,' even though production of monoclonal antibodies necessary to practice invention first requires production and screening of numerous antibody producing cells or 'hybridomas,' since practitioners of art are prepared to screen negative hybridomas in order to find those that produce desired antibodies, since in monoclonal antibody art one 'experiment' is not simply screening of one hybridoma but rather is entire attempt to make desired antibody, and since record indicates that amount of effort needed to obtain desired antibodies is not

excessive, in view of Applicants' success in each attempt to produce antibody that satisfied all claim limitations.

Wands at 1400. Thus, the need for some experimentation does not render the claimed invention unpatentable under 35 U.S.C. § 112, first paragraph. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

In summary, the presently rejected claims are directed at a host cell not their use in gene therapy. The Examiner has erroneously construed the claims to be directed at the use of a host cell in gene therapy, not the host cell itself. The present specification and the state of the art are fully enabling for the scope of the instant claims which are directed at a host cell.

Hundreds of claims to host cells comprising a vector comprising a particular nucleotide sequence are regularly allowed by United States Patent and Trademark Office and as issued U.S. Patents are presumed to meet all of the requirements for patentability, including enablement under 35 U.S.C. §112, first paragraph. Furthermore, Applicants believe that gene therapy is not a procedure that should have been properly construed to fall within the reasonable scope of the present claims. Therefore, Applicants respectfully submit that the present claims directed at host cells are fully enabled and request withdrawal of the pending rejection under 35 U.S.C. §112, first paragraph.

IV. Conclusion

The present document is a full and complete response to the Action. In conclusion,

Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Murphy have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

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